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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,664	08/17/2001	Denise L. Faustman	DLF-002.1P	4530

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EXAMINER

AFREMOVA, VERA

ART UNIT

PAPER NUMBER

1651

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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/913,664

Applicant(s)

FAUSTMAN, DENISE L.

Examiner

Vera Afremova

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 25 June 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-14 and 16-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1-14 and 16-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

Status of claims

Claims 1-14 and 16-23 as amended are under examination in the instant office action.

Claims 15 and 24-37 are canceled by applicant. [Paper No. 11 filed 6/25/2003].

Response to Arguments

Applicant's arguments filed 6/25/2003 [Paper No. 11] have been fully considered but they are not persuasive for the reasons below.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3 and 5-8 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by US 4,399,123 [IDS-AB].

Claims are directed to a method for inhibiting rejection by a host mammal of another mammal donor tissue wherein the method comprises step of treating a viable donor tissue with an enzyme effective for removing MHC Class I antigen and step of transplanting and maintaining the treated viable tissue in the host mammal. Some claims are further drawn to donor and host mammals belonging to the same species or to the different species. Some claims are further drawn to the use of tissues such as skin cells. Some claims are further drawn to the use of a second enzyme to remove antigenic surface structure form the donor tissue.

US 4,399,123 is relied upon as explained in the prior office action and repeated herein.

US 4,399,123 discloses a method for inhibiting rejection of donor tissue (example 1) wherein the method comprises step of treating a mammalian donor tissue with first proteolytic

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enzyme (col. 6, line 52) and with second carbohydrate splitting enzyme (col. 6, line 53) in order to remove antigenic structures including antigenic glycoproteins and polysaccharides (col. 2, line 15) and steps of transplanting and maintaining the enzyme treated donor tissue in the other mammalian host (col. 6, line 57). The particular enzymes are trypsin or chymotrypsin and amylase (examples 1-4). The cited patent also teaches that the other suitable proteolytic enzymes include papain (col. 2, lines 63-64). The transplant tissues are selected from human or animal dermis, tendon and ligament tissues (examples 1-4). The cited patent teaches that the enzyme treated donor tissues including human or animal tissues are suitable for both homo- and hetero-transplantations in the method for inhibiting transplant rejection and ablating recipient immune response (col. 2, lines 1-45 or example 1).

The cited patent US 4,399,123 is considered to anticipate the claimed invention because it teaches identical method for inhibiting transplant rejection comprising identical active steps of treating and transplanting donor tissues and identical structural elements including two enzymatic treatments and various combinations of donor tissues and host organisms as the claimed method. Although the cited patent does not clearly point out the removal of MHC Class I antigenic molecules, it teaches an enzyme treatment of donor tissue for the same purpose of removal of antigenic groups or molecules. Therefore, the cited method is reasonably expected to result in the removal of glycoproteins such as MHC Class I molecules particularly in view that two identical types of enzymes such as proteolytic and carbohydrate splitting enzymes are used for removal of antigenic structures including glycoproteins (col. 2, line 16). Moreover, the cited patent teaches that after transplantation into the host mammal of the enzyme treated donor tissue there were no evidence of lymphocytes infiltration (col. 6, line 61) and, thus, the treated

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transplant tissue has been at least “temporarily” rendered resistant to immune-mediated attack by the host’s immune system within the scope of the presently claimed invention.

Applicant’s main argument is directed to the newly introduced limitation such as viability of donor tissue in the method for tissue transplantation and inhibiting rejection by a host recipient of a donor tissue (response page 12, lines 4-5). Applicant argues that the donor tissue in the method of the cited patent US 4,399,123 is dead or it is not viable because the donor tissue has been treated with lethal compound such as sodium azide (response page 9, par. 2) and because the donor tissue has been cross-linked with glutaraldehyde (response page 9, par. 3).

However, upon review of the teaching of the cited patent US 4,399,123 it is established that the cited patent US 4,399,123 does not disclose that the donor tissue is rendered dead or non-viable as the result of treatment before transplantation. US 4,399,123 clearly teaches that sodium azide is used as “bactericide” (col. 6, line 50) which is reasonably expected to achieve elimination of a possible pathogen transmission during transplantation rather than to render the donor tissue dead or non-viable. The presently claimed method is also reasonably expected to include at least some tissue sterilization protocols by the virtue of the open language “comprising”.

Further, US 4,399,123 clearly teaches that the cross-linking with glutaraldehyde is intended for removal of antigenicity in the donor tissues (col. 3, line 60-65) and, thus, this treatment is intended for inhibiting rejection by host mammal of donor tissue from another mammal as encompassed by the claimed invention. Although it could be true that the viability of the donor tissue might have been reduced or “temporarily” reduced by the glutaraldehyde cross

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linking, the cross-linked tissue remains viable at least to some extent. The following references are cited for support of argument. For example: US 6,322,593 discloses that the viability of the tissue intended for transplantation is 7-20% after 5-16 hours treatment with 0.25% glutaraldehyde (table 1). The method of the cited patent US 4,399,123 discloses the use of 0.01% glutaraldehyde which is less than 0.25% and, thus, it is not a "harsh" treatment as argued by applicant, for example. The reference by Gallagher et al teaches that the monocytes which are mildly fixed with glutaraldehyde remain viable and that they have unaltered surface antigen expression (abstract). Thus, the mild tissue cross-linking treatment is expected to allow for a future expression and/or re-expression of surface antigens including MHC Class I in the treated tissue as encompassed by the claimed method and as also argued by applicant with respect to the idea of re-education of the host' immune system (response page 14, par. 4).

Applicant also argues that the goal of the cited patent US 4,399,123 is a retention of matrix structure of the donor tissue rather than stimulation of tolerance by the host of the donor tissue after transplantation as encompassed by the applicants' invention (response pages 10-11). However, it is noted that the concept of "tolerance" or of the host immune system "re-education" is not within the invention as claimed. Further, although the applicant's generic disclosure might suggest this concept as a possible mechanism of action (page 6, par. 2) , it is not supported by the exemplified disclosure (examples 1-4). Moreover, applicant admits that knowledge of exact amount of time the donor tissues takes in re-establishing normal surface expression is not necessary to practice the invention and that it is a natural processes which is largely out of the control of the practitioner (response page 8, par. 1-2).

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Therefore, the cited patent is still considered to anticipate the presently claimed method for inhibiting rejection by a host mammal of donor tissues because it teaches the same enzymatic treatment of a viable donor tissue for the same purpose of removal of antigenic groups or molecules and the same steps of transplanting and maintaining the treated viable donor tissues in the host as the claimed method.

Claims 1-3, 5-7, 9 and 12 as amended remain rejected under 35 U.S.C. 102(b) as being anticipated by US 5,397,353 [A].

Claims are directed to a method for inhibiting rejection by a host mammal of a donor tissue transplant derived from another mammal wherein the method comprises step of treating a viable donor tissue with an enzyme effective for removing MHC Class I antigen such as papain and steps of transplanting and maintaining the treated donor tissue into/in the host mammal. Some claims are further drawn to donor and host mammals belonging to the same or to the different species. Some claims are further drawn to the use of tissues such as skin or skin cells. Some claims are further drawn to the second transplanting step in the method for inhibiting transplant rejection.

US 5,397,353 [A] is relied upon as explained in the prior office action and repeated herein.

US 5,397,353 [A] discloses a method for inhibiting rejection by a host mammal of a donor tissue transplant derived from another mammal wherein the method comprises step of treating a mammal donor tissue with an enzyme effective for removing MHC Class I antigen such as papain (col. 6, line 20), step of transplanting the treated tissue into a host mammal (col.

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6, line 30) and second transplanting step (col. 6, line 40-41). The method of the cited patent is applied to mammals belonging to the same and/or to the different species including pigs and rats in a particular example (col. 6, line 14, 30 and 41). The transplantation of the enzyme treated tissues result in elicitation of immunological reaction (col. 6, line 34; col.5, line 14). The cited patent teaches applicability of the method of inhibiting transplant rejection for both human and animal tissues for both homo-and hetero-transplantations (col. 3, lines 26-28). It also encompasses optional treatment with second type of enzyme or with a carbohydrate-splitting enzyme effective for removal of antigenic moieties of polysaccharide nature (col. 4, lines 65-68).

The cited patent US 5,397,353 is considered to anticipate the claimed invention because it teaches an identical method for inhibiting transplant rejection comprising identical active steps of papain enzymatic treatment of donor tissues and two steps of transplanting. Although the cited patent does not clearly point out that the papain treatment results in the removal of MHC Class I antigenic molecules, it teaches the use of enzymatic treatment including papain treatment for the same purpose as the presently claimed invention such as removal of antigenic groups or molecules and inhibiting immune response in transplant recipient. Therefore, the cited method is reasonably believed to result in the removal of the same glycoproteins including MHC Class I molecules particularly in view that the identical papain enzyme is applied to the donor tissues and in view that the immunological reactions were absent or elicited after transplantation of papain treated donor tissue. Thus, the method for inhibiting transplant rejection of the cited patent results in ablating, at least temporarily, of the immune-mediated attack by the host's immune system within the scope of the presently claimed invention.

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With respect to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 5,397,353 [A] all applicant's arguments are the same and/or similar as applied to the claim rejection over the teaching of US'123 and they are directed to the newly introduced limitation such as viability of donor tissue in the method for tissue transplantation and inhibiting rejection by a host recipient of a donor tissue (response pages 12-14).

Upon review of the teaching of the cited patent US 5,397,353 is it established that the cited patent US 5,397,353 does not disclose that the donor tissue is rendered dead or non-viable as the result of treatment before transplantation. The sodium azide is used as "bactericide" (col. 6, line 23) but not to render the donor tissue dead or non-viable. The cross-linking treatment with hexane diisocyanate is used for removal of antigenicity (see col. 3, lines 53-57) as the glutaraldehyde treatment in the method of US'123. Therefore, the donor tissue in the method of the cited patent US 5,397,353 is not dead and/or it is considered to be "viable" or capable either re-establish expression of surface antigen after transplantation or to re-educate the host immune system in order to inhibit the transplant rejection within the meaning of the claims and as argued. The "architectural" characteristics that are argued can not be considered as indication of a dead tissue and the absence of hair on the transplanted skin grafts that is argued can not be considered as indication of a permanent loss of antigenic protein expression (response page 13).

Therefore, the cited patent US 5,397,353 is still considered to anticipate the presently claimed method for inhibiting rejection by a host mammal of donor tissues because it teaches the same enzymatic treatment of a viable donor tissue for the same purpose of removal of antigenic groups or molecules and the same steps of transplanting, maintaining and second transplanting the treated viable donor tissues in the host as the claimed method.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-9 and 12-23 as amended remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR].

Claims are directed to a method for inhibiting rejection by a host mammal of a donor tissue transplant derived from another mammal wherein the method comprises step of treating a viable donor tissue with an enzyme effective for removing MHC Class I antigen and steps of transplanting and maintaining the treated viable tissue into/in the host mammal. Some claims are further drawn to donor and host mammals belonging to the same or different species. Some claims are further drawn to host mammal being human. Some claims are further drawn to the use of tissues cells and/or organs including skin, blood and/or lymphocytes. Some claims are further drawn to the second transplanting step in the method for inhibiting transplant rejection. Some claims are further drawn to specific time and concentration for papain treatment of the donor tissue in the method for inhibiting transplant rejection.

The cited patents 4,399,123 [IDS-AB] and US 5,397,353 [A] are relied upon as explained above for the disclosure of methods for inhibiting transplant rejection wherein the method comprises steps of treating a mammal donor tissue with enzymes effective for removal of antigenic molecules including antigenic glycoproteins and polysaccharides and step of transplanting the treated tissue into host mammal.

The particular enzyme which is employed for the removal of antigenic moieties is papain in the method of US 5,397,353 and the cited US 5,397,353 also teaches time and concentration of papain for treating donor tissue in the method for transplantation and inhibiting transplant

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rejection. The cited patent US 4,399,123 teaches the equivalency of proteolytic enzymes including trypsin and papain in the method for inhibiting transplant rejection.

The exemplified method of the cited US 4,399,123 comprises one transplanting step. But the exemplified method for inhibiting transplant rejection of the cited US 5,397,353 comprises two transplanting steps.

Both cited patents teach and suggest donor tissue enzymatic treatment with two types of enzymes in the methods for inhibiting transplant rejection as explained above.

Both cited patents teach and suggest applicability of the disclosed methods for both human and animal donor tissues and for both homo-and hetero-transplants as explained above.

Although the cited patents US 4,399,123 [IDS-AB] and US 5,397,353 [A] do not clearly point out that the enzymatic treatment with proteolytic enzymes including papain is responsible primary for the removal of MHC Class I antigenic molecules in the method for inhibiting transplant rejection, they either clearly teach {US 5,397,353} or suggest {US 4,399,123} the use of a papain treatment of donor tissue transplants in the methods for inhibiting transplant rejection. The cited patents also clearly teach the necessity of removal of antigenic glycoproteins for inhibiting transplant rejection.

Further, the reference by Galati et al. [IDS-AR] clearly and particularly demonstrates that papain removes MHC Class I molecules of glycoprotein nature from cell surface (abstract) and it teaches that the MHC class I glycoproteins are expressed on nearly all nucleated cells, thus, including all mammalian cells (page 77, col. 1, par. 2). It also teaches that other than the MHC class I surface associated molecules remain unaffected by papain digestion (page 79, col. 1, last par.). In particular, the reference by Galati et al discloses treatment of blood cells or lymphocytes with papain for removal of the MHC class I antigens.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use papain for removal of MHC class I antigens in the

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method for inhibiting transplant rejection with a reasonable expectation of success in at least temporarily ablating immune response of transplant recipient as taught and/or suggested by the cited patents US 4,399,123 [IDS-AB] and US 5,397,353 [A] because papain tissue treatment results in disappearance of MHC class I glycoprotein antigens from surface membrane of all cells and/or tissues while in affecting other surface membrane associated molecules as clearly taught by Galati et al. [IDS-AR]. The use of human and/or animal donor tissues for homo- and hetero-transplants would have been obvious to one having ordinary skill in the art at the time the claimed invention was made as clearly suggested by both cited patents US 4,399,123 [IDS-AB] and US 5,397,353 [A]. Further, incorporation of second transplanting step in the method for inhibiting transplant rejection is considered to be within the purview of one having ordinary skill in the art of surgery depending on a particular surgery design and/or transplantation needs of a particular host mammal. It is considered to be within the purview of one of ordinary skill in the art to adjust time and concentration of enzymes including papain for treating donor tissues and for removal of antigenic molecules. Applicant admits that the practitioner would be able to adjust time and concentration to optimize the desired result (specification page 7, lines 19-21). Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

With regard to the claim rejection under 35 U.S.C. 103(a) as being unpatentable over US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR] applicant argues that the reference by Galati does not mention a transplantation of papain treated tissue (response page 15, last par.). However, this reference is relied upon to demonstrate that the papain enzyme removes antigenic structures that are the MHC Class I antigens as encompassed by the claimed

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invention. The transplantation of the papain treated donor tissues is taught by the cited patents US 4,399,123 and US 5,397,353 combined. Thus, the prior art teaches and suggests all claimed limitations.

Applicant also appears to argue that the cited patents US 4,399,123 and US 5,397,353 are unrelated to the novel method taught in the present application (response page 15, par. 2). This is not found true with respect to the claimed invention for the reasons as explained above.

Claims 10 and 11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR] as applied to claims 1-9 and 12-23 above, and further in view of Stone et al. [IDS-BJ].

Claims 1-9 and 12-23 as explained above. Claim 10 is further drawn to the second enzyme being galactosidase in the method for inhibiting transplant rejection. Claims 11 is further drawn to the use of two particular enzymes such as papain and galactosidase together in the method for inhibiting transplant rejection.

The cited references US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR] are applied as explained above for the teaching of a method for inhibiting transplant rejection comprising treating the viable donor tissue with two type of enzymes such as a proteolytic including papain for removal of the MHC class I antigens of glycoprotein natures {US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR]} and carbohydrate-splitting enzyme for removal of antigens of polysaccharide nature {US 4,399,123 [IDS-AB] and US 5,397,353 [A]}.

Although the cited patents US 4,399,123 [IDS-AB] and US 5,397,353 [A] teach the use of second carbohydrate-splitting enzyme for removal of antigens of polysaccharide nature they are missing disclosure about galactosidase.

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But the reference by Stone et al. [IDS-BJ] discloses a method for inhibiting transplant wherein the method comprises step of treating donor tissue with galactosidase and step of transplanting the treated tissue in to host recipient and wherein the method results in a reduction of inflammatory reaction or immune response of recipient host (pages 1577-1578 at paragraphs "Methods" and "Conclusions").

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use galactosidase of the reference by Stone as a carbohydrate-splitting enzyme in the methods for inhibiting transplant rejection of US 4,399,123 [IDS-AB] and/or US 5,397,353 [A] with a reasonable expectation of success in removal of antigenic molecules having polysaccharide nature because tissue treatment with galactosidase results in the removal of carbohydrate-containing antigenic epitopes and in the reduction of host immune reaction as taught by Stone et al. [IDS-BJ]. One of skill in the art would have been motivated to use a combination of a proteolytic enzyme including papain and a carbohydrate-splitting enzyme including galactosidase for the removal of both types of antigens including MHC class I antigens of glycoprotein nature and antigens of carbohydrate or polysaccharide nature for the expected benefit in the reduction and/or inhibiting immune response of the donor tissue recipient as adequately demonstrated by all the cited references. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

With respect to the claim rejection over US 4,399,123 [IDS-AB] and US 5,397,353 [A] taken with Galati et al. [IDS-AR] as applied to claims 1-9 and 12-23 above, and further in view of Stone et al. [IDS-BJ] applicant appear to argue that the reference by Stone teaches a permanent removal of alpha-gal epitopes but not a re-appearance of MHC Class I antigens after

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transplantation in order to "re-educate" host immune response (page 17). Yet, the claimed invention does require alpha-galactosidase treatment in combination with papain and it does not require "re-education" as argued.

Conclusion

No claims are allowed for the reasons as explained above.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

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September 12, 2003.



SANDRA E. SAUCIER
PRIMARY EXAMINER